Exhibit 7

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Talc: Consumer Uses and Health Perspectives[1]

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EXECUTIVE SUMMARY

This issue of the journal is largely dedicated to report on a January 31–February 1, 1994 workshop on talc, organized under joint sponsorship of the U.S. Food and Drug Administration (FDA), the Cosmetics, Toiletries, and Fragrances Association (CTFA), and the International Society of Regulatory Toxicology and Pharmacology (ISRTP). Although not all papers given at the meeting were made available for publication, this offers a general overview of the substance of the presentations and discussions.

The workshop was to provide a forum for an updated discussion of the origins, manufacture, characterization, toxicology, and epidemiology of talc. Principal focus of the meeting was on the latest toxicologic and epidemiologic studies, as they reflect on the safe uses of talc in consumer products. The characteristics of cosmetic-grade talc, the history of its uses in a variety of products, and the current quality-control measures to ensure safety were followed by a review of the regulatory history of talc and by an appraisal of recent National Toxicology Program (NTP) studies of chronic pulmonary exposure of rodents to talc.

Of special interest was the relevance of these studies to human risk assessment, in view of reported technical problems of lung overload for these bioassays, and of the standing concerns about the physiologic, anatomic, genetic, and other differences of rodents and man. Experimental data were then evaluated against the contrasting evidence emerging from epidemiologic studies of human talc exposure. A critical panel of invited experts and speakers completed each session. Faculty and panelists included talc mineralogists, geologists, toxicologists, epidemiologists, pathologists, food/drug/cosmetic/medical device manufacturers, qualified regulatory specialists, and consumer representatives.

In brief opening remarks, Dr. John E. Bailey (FDA) reminded participants that the workshop was not part of a formal rule-making process and could not be a forum to reach a consensus for regulatory decisions. Emphasis was to be on a free interaction between participants to explore and possibly reach some conclusion on the validity and significance of the existing knowledge regarding the safety of cosmetic talc.

A first and essential presentation by Dr. Gettings (CTFA) addressed conclusively the nature of cosmetic talc, the specific form of talc under study now recognized in the 1990 U.S. Pharmacopoeia, and other official standards. Unique physical and chemical properties—inertness, hygroscopicity, self-aggregation, lubrication, tactile sensation, translucency, and color—make powdered talc desirable, useful, and virtually indispensable in cosmetic applications. Cosmetic talc is a negligible fraction of the nearly 50,000 tons mined for industrial use in the United States and today stringent safety and quality-control measures ensure the absence of asbestos fibers formerly considered as a potential hazard, albeit not a defined one.

Dr. Gilbertson (FDA) reviewed the harmonization of international standards and regulations for cosmetic talc and its consumer applications. In their joint evaluation, talc has proven to be among the safest of all consumer products.

In addressing fundamental aspects of inhalation toxicology, Dr. Oberdörster (Rochester University) noted that any inhaled dust—and most substances for that matter—may cause inflammation and cell proliferation in the lung, possibly leading to tumor formation if the challenge is sufficiently strong and persistent to overcome the natural defenses of the animals under test. This condition implies the presence of a no-effect threshold at levels below which natural defenses remain functional to prevent tumor formation. He noted that the NTP inhalation bioassays of talc invariably created lung overloads, thus making the interpretation of results quite problematic. In his overall evaluation of the toxicologic literature on talc, there is no reason for concern for low-level uses of cosmetic talc.

As a staff scientist of the National Toxicology Program, Dr. Boorman emphasized that NTP protocols call for maximum tolerated doses (MTDs) in an attempt to identify any hazards. Negative findings may receive little or no further attention, but positive ones call for detailed mechanistic studies to determine their relevancy for human health. In a detailed description of the talc inhalation bioassays at NTP, their protocol, and pathology findings, he concurred with evidence of dose overloads in most of the animals that ended up developing tumors. He explained the lack of an ovarian effect of lifetime exposure in F344/14 rats and B6C3F1 mice. In his summary report he notes the many factors that complicate interpretation of these rodent studies.

The results of the NTP inhalation bioassays on talc were first evaluated as customary in 1992 by the Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors. Dr. Goodman (Michigan State

University)—a member of that review—reported on events that transpired during that review, which concurred with NTP staff the recommendations, namely that talc was to be listed as a carcinogen even though it caused lung tumors in female rats only, pheochromocytomas in male and female rats, and no tumors in mice. Dr. Goodman recalled being the single member to vote against this motion. His dissent derived from the obvious overload conditions of the high-dose animals—no tumor elevation was observed at the low dose (NOAEL threshold)—and from more general objections to the lack of mechanistic input in the standard protocols and bioassay evaluation procedures by NTP. During his tenure on the NTP Board of Scientific Advisors, Dr. Goodman participated in an official review of the NTP bioassay methods and procedures, as the Chair of the carcinogenesis working group. This review resulted in a report (*Fed. Reg.* **57,** 31721–31730, 1992) that emphasized the need to change the standard bioassay so as to incorporate mechanistic studies in order to provide the biological information that is required to take a rational approach to risk assessment.

Dr. Kuschner (State University New York) reviewed in detail many of the issues of the relevance of the results of the rodent bioassays to human beings and Dr. Crapo (Duke University) explained present knowledge of species differences in lung physiology that influences the toxicity of inhaled substances. These reports were followed by Dr. Mossman (University of Vermont) who reviewed the cellular pathology in animals and man as influenced by inhaled particles, especially many kinds of well-known dusts, the effects of smoke inhalation, asbestos, and other kinds of mineral-induced particles' toxicity related to lung disease. It was obvious that talc particles are fundamentally different than such materials as chrysotile asbestos. It was evident from the many hypotheses describing the mechanisms of lung toxicity caused by such things as titanium dioxide and carbon black that high exposure levels are very different from the lower exposures that humans have. This strongly suggests that one should be careful in relating these to cosmetic talc exposure. At one point there seemed to be general agreement in the discussions that the rodent data on talc exposure were not relevant to human inhalation toxicity.

In the panel discussion following these papers a novel idea emerged. Is it possible to use some nontoxic, "inert" particulate in the airway of rodents to serve as a negative control? Or is there a positive, active "model" control that produces a true carcinogenic response in comparison with an unknown test substance?

Several cogent questions were asked without answer: What is the level of uncertainty? Are there agreed upon mechanisms? How different are adults from small 1- to 2-year-old children when exposed to cosmetic talc?

In a summary of such a comprehensive review of whether data from chronic bioassays in rodents can be used to predict human cancer risk, Dr. Gori (ISRTP) suggested that presentations and discussions made it clear that this question is unlikely to have a scientific answer. This is because our mechanistic understanding of cancer pathogenesis is rudimentary and still hypothetical, while the single most significant advance during the past 10 to 15 years is an appreciation of the many complex and variable pathways that may lead from normalcy to malignancy.

This appreciation may have begun to liberate our way of thinking from the traditional naive generalizations of initiation, promotion, one hit models, and so on. We may begin to see cancer as a more complex phenomenon arising from multiple interactions of intra- and extracellular stressors—biotic and xenobiotic—with genetic and epigenetic operants in multiple cascades of events that may take from months to entire lifetimes before clinical cancer—the only truly significant cancer—develops. Dr. Gori recalled the report prepared by the NTP Board of Scientific Advisors in 1992 in which Dr. Goodman chaired the carcinogenesis working group—mentioned above—as a masterful primer about the persisting mechanistic ignorance that prevents a scientific or even a reasonable use of rodent bioassays for determining human cancer risks: "Can we trust as a human risk predictor a test that has only a 70% concordance between rats and mice? And this despite the use of test doses that regularly exceed physiologic tolerances? A process that usually labels carcinogens by partial consensus of a panel of reviewers, so controversial can the data be?"

"In the specific case of talc, the particle size of the powder used was not realistic. The MTD guidelines were exceeded with clear signs of chronic toxicity in the tumor-bearing female rats. There is no concordance of rat and mouse outcomes and there is no concordance of male and female rat outcomes." Drs. Kushner, Crapo, and Mossman spoke convincingly of the fundamental anatomic and physiologic differences and of the different responses of rat and human lungs. "Speaking scientifically—and if we forget for a moment epidemiologic data—the rodent data seem unable to tell us whether talc is or is not a human carcinogenic risk."

"Of course, knowledgeable people can express an opinion, and we do have a number of comforting experimental clues—the low acute toxicity and apparent lack of mutagenicity of talc, negative bioassay results in rodents despite exorbitant doses, and an adequate understanding of lung clearance rates in humans and of their capacity to dispose of exposures below certain threshold limits. To reasonable people—even armed with reasonable concern for prudence—these clues suggest that the probability of human risk is likely nonexistent under customary conditions of use." On the other hand, human epidemiologic studies could seem more probative, because of the lack of problems of species extrapolation, maximum tolerated doses, overloads, physiologic and anatomical differences, and so on. Is the interpretation

of epidemiologic studies more straightforward and direct?

Unfortunately—Dr. Gori suggested—epidemiology presents a new set of impediments. The epidemiology we are facing does not offer the same direct cause and effect associations typical of infectious diseases. Human cancers are multifactorial diseases arising from a combination of simultaneous exposures to many potential etiologic determinants. To extricate the significance of any one of these factors from the integrated effects of all others is a challenging task. If one adds the technical problems in the execution of these studies, we soon find that the epidemiologic fog is just as difficult to penetrate as the one generated by animal bioassays. Kenneth Rothman (1986), a leading theoretician of American epidemiology, has reviewed extensively these difficulties of interpretation of causal inferences and writes:

> Despite philosophic injunctions concerning inductive inference, criteria have commonly been used to make such inferences. The justification offered has been that the exigencies of public health problems demand action and that despite imperfect knowledge causal inferences must be made.

This definition is widely accepted by mainstream epidemiologists today. On this basis however—just as we could ask whether extrapolation from animal bioassays qualifies as a scientific exercise—we are justified in asking the same question of human epidemiology.

In a general overview of ovarian cancer epidemiology, Dr. Austin (Emory University) noted the many factors that may confound the putative association of perineal talc exposure and ovarian cancer. Following a presentation by Dr. Brown (University of Wisconsin), the discussion made it clear that available histologic and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region.

Dr. Hartge (National Cancer Institute) and Dr. Harlow (Harvard University) presented a review of epidemiologic studies—including their own original studies—pertaining to perineal talc exposure and ovarian cancer risk. The studies reviewed brought to light the many interpretive difficulties of epidemiology as an observational science and are detailed in the papers by Drs. Hartge and Harlow appearing in this issue of the journal. From the unique perspective of his long and distinguished experience in the epidemiology of multifactorial diseases, Dr. Wynder (American Health Foundation) reviewed the history of the evolutionary processes that provided natural defense systems against disease. He stressed the specific problems in the epidemiology of weak associations: biases of respondents and investigators, known and unknown confounding factors, and the irresistible urge to interpret results as if only a reduced set of variables of interest was operant, without acknowledging and controlling for a more complex multifactorial reality. Following the many issues raised by all presenters, the ensuing discussion generally agreed that while some weak association between talc exposure and ovarian tumors has been reported, it was not sufficient warning for concern.

A final panel included most speakers and other experts and was able to reach an unanimous assessment of the workshop. In regard to the NTP talc bioassay in rodents, it found that because of the extreme doses and the unrealistic particle sizes of the talc employed, because of the negative results in mice and male rats, because of the lack of tumor excess at the low doses, and because of the clear biochemical and cytological markers of excessive toxicity in female rats, the positive talc bioassay results in female F344/N rats are the likely experimental artifact and nonspecific generic response of dust overload of the lungs and not a reflection of a direct activity of talc. Given the gross differences of rodent and human lungs, the lung clearance capabilities of humans, and the possible conditions of customary human exposures, the NTP bioassay results in F344/N female rats cannot be considered as relevant predictors of human risk.

In regard to the proposed association of talc exposure and ovarian cancer, the panel found that epidemiologic data are conflicting and remain equivocal. Although it is theoretically possible that talc could reach the ovaries, the actual access to or the presence of talc in ovarian tissue is not documented. Diet, parity, contraceptive use, ovulatory frequency, familial predisposition, age to menarche and menopause, and other factors associate strongly and plausibly with ovarian cancer incidence. These possible confounders and control selection biases, publication biases, interviewer and interviewee biases, and other factors may well explain the conflicting results that have appeared in the literature.

The possibility of an association of talc exposure and ovarian cancer is an important hypothesis of potential public health importance. However, this association remains a research hypothesis whose verification or falsification needs additional study. Experimental studies may be needed to determine whether talc could access the ovaries under field conditions and, if so, whether it could be embedded in ovarian tissue and produce pathologic effects. For epidemiology, further refinements may be possible in the selection and characterization of control subjects and in the accounting of possible confounders and biases. However, epidemiologic studies have provided weak and conflicting risk signals for this association, and it is unlikely that further studies may prove adequate to raise concern at a level sufficient to warrant regulatory or public health measures.

REFERENCE

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